3-19-2020

Proteinuria

Goni Katz-Greenberg, MD
Thomas Jefferson University

Jefferson
Philadelphia University +
Thomas Jefferson University

Proteinuria

Goni Katz-Greenberg, MD
Transplant Nephrology Fellow

Outline and objectives

DEFINITION

SCREENING/ MEASUREMENT

ETIOLOGY

TREATMENT

Definition of Proteinuria

- Normal protein excretion < 150mg daily
- Normal albumin excretion < 30mg daily
- Moderately increased albuminuria 30-299mg daily (formerly microalbuminuria) over 3-6 months*
- Severely increased albuminuria > 300mg daily (formerly macroalbuminuria)
- Nephrotic range proteinuria > 3.5 grams daily

Measurement of Proteinuria

- Albumin excretion above 300 mg/day is considered overt albuminuria → the level at which the standard dipstick becomes positive
- Dipstick – ALBUMIN

- 24-hour urine test - gold standard, but cumbersome
- Urine protein:creatinine ratio/ spot ratio

24-hour urine collection

- The **gold standard** for measurement of protein excretion is a 24-hour urine collection (normal value <150 mg/day).
- Adults under the age of 50 years, daily creatinine excretion should be
  - 20 to 25 mg/kg of lean body weight in men
  - 15 to 20 mg/kg of lean body weight in women
- From the ages of 50 to 90 years, there is a progressive 50% decline in creatinine excretion due primarily to a fall in muscle mass

UPCR

- UPCR best done as spot first- or second-morning urine sample after avoiding exercise
- It is a RATIO, and is best when done in a steady state
- Individuals with large muscle mass, the UPCR (or UACR) will **underestimate** proteinuria
- In cachectic/small muscle mass patients, the UPCR (or UACR) will **overestimate** proteinuria

Case 1

Mr. Jones is a 69 years old male who comes to clinic complaining of increased abdominal girth and leg swelling for the past 4 weeks. His other PMHx is significant for HTN and hyperlipidemia.

Physical exam -

- Temperature 37.2C (98.9)
- BP 135/68, HR 85
- HEENT – WNL
- Chest – clear to auscultation
- Heart – S1S2, no murmurs or gallops
- Abdomen – distended, non tender
- LEs – Edema +3 bilaterally, to hip level

Case 1 – Cont'd – Differential Diagnosis

- Nephrotic Syndrome
- Cirrhosis
- Heart failure
- Myxedema

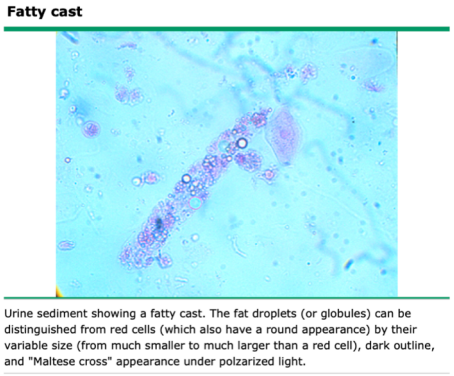
Case 1 – Cont'd – Work up

- Albumin
- BUN, creatinine
- Urinalysis
- 24-hour urine protein/ UPCR in random sample
- Serum LDL and cholesterol
- LFTs ?

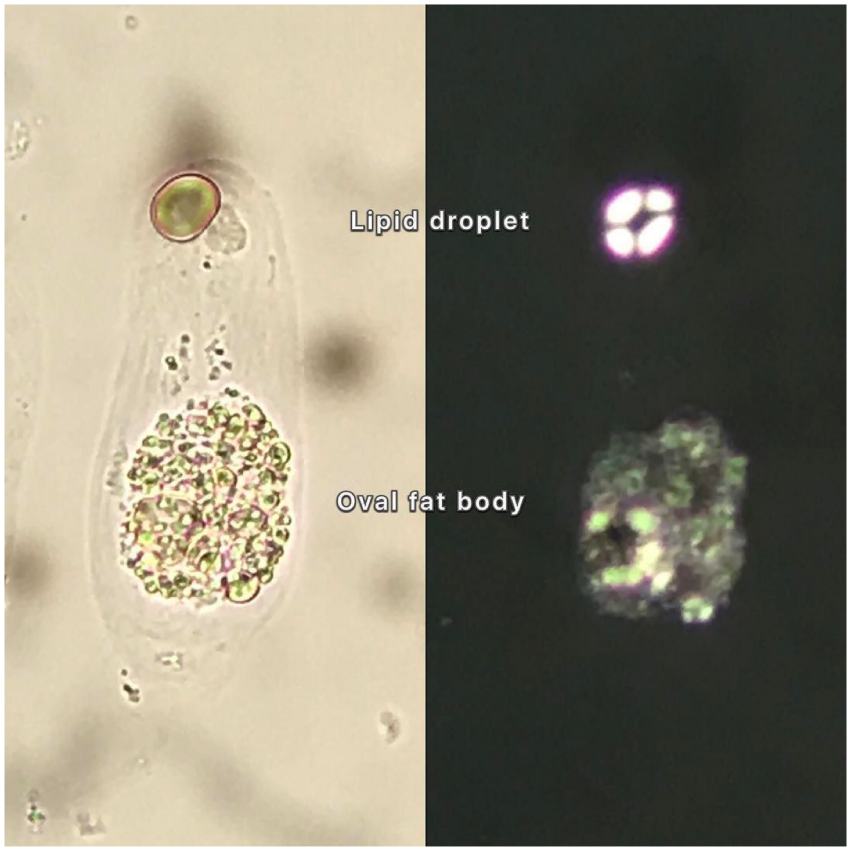
Albumin	2.8g/dL
Creatinine	1.1mg/dL
BUN	25
Urinalysis	+ 4 protein, with oval fat bodies seen. Few RBC, no casts.
UPCR	8.5g/g
T. chol	310 mg/dL

Nephrotic Syndrome

- Urine protein exertion of > 3.5 gram/ 24 hours (or UPCR of > 3000mg/g)
- Hypoalbuminemia < 3.0 g/dL
- Edema
- Hyperlipidemia +/- Lipidiuria



Urine sediment showing a fatty cast. The fat droplets (or globules) can be distinguished from red cells (which also have a round appearance) by their variable size (from much smaller to much larger than a red cell), dark outline, and "Maltese cross" appearance under polzarized light.



Where is the proteinuria coming from?

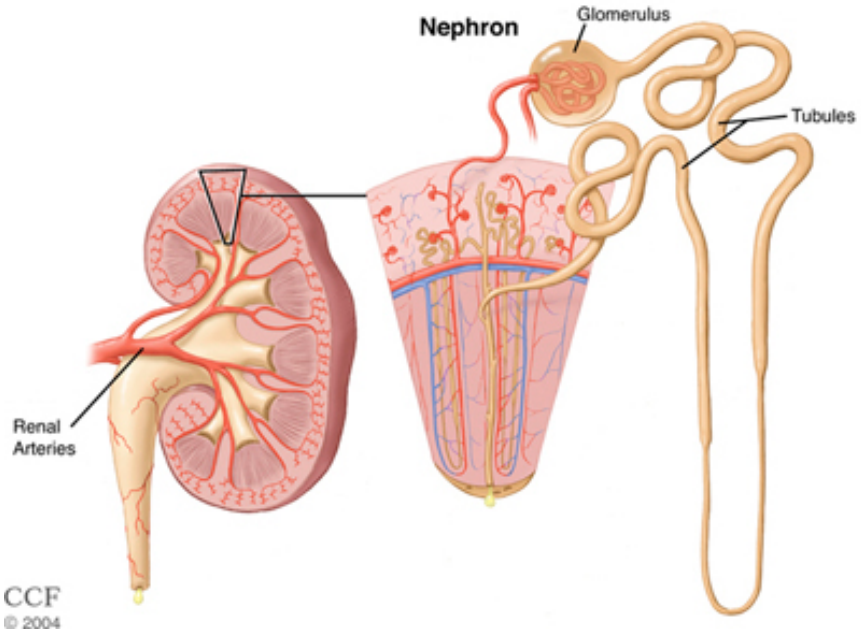
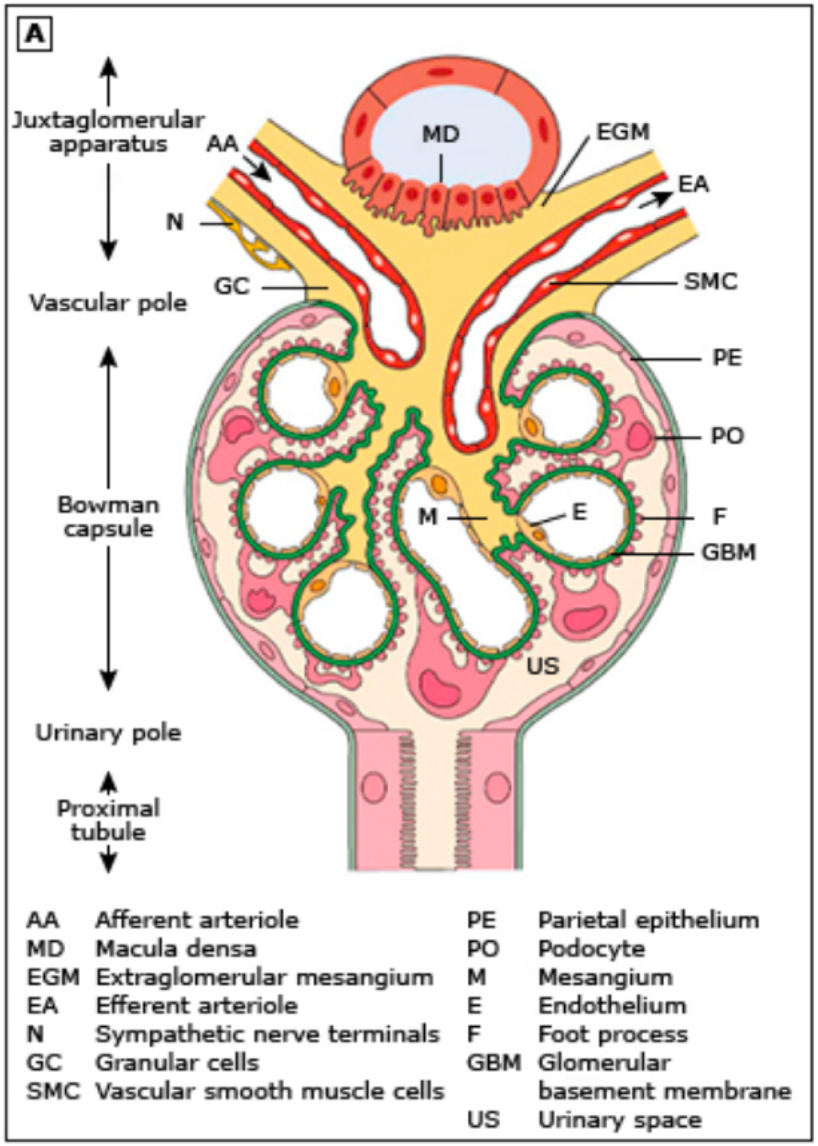
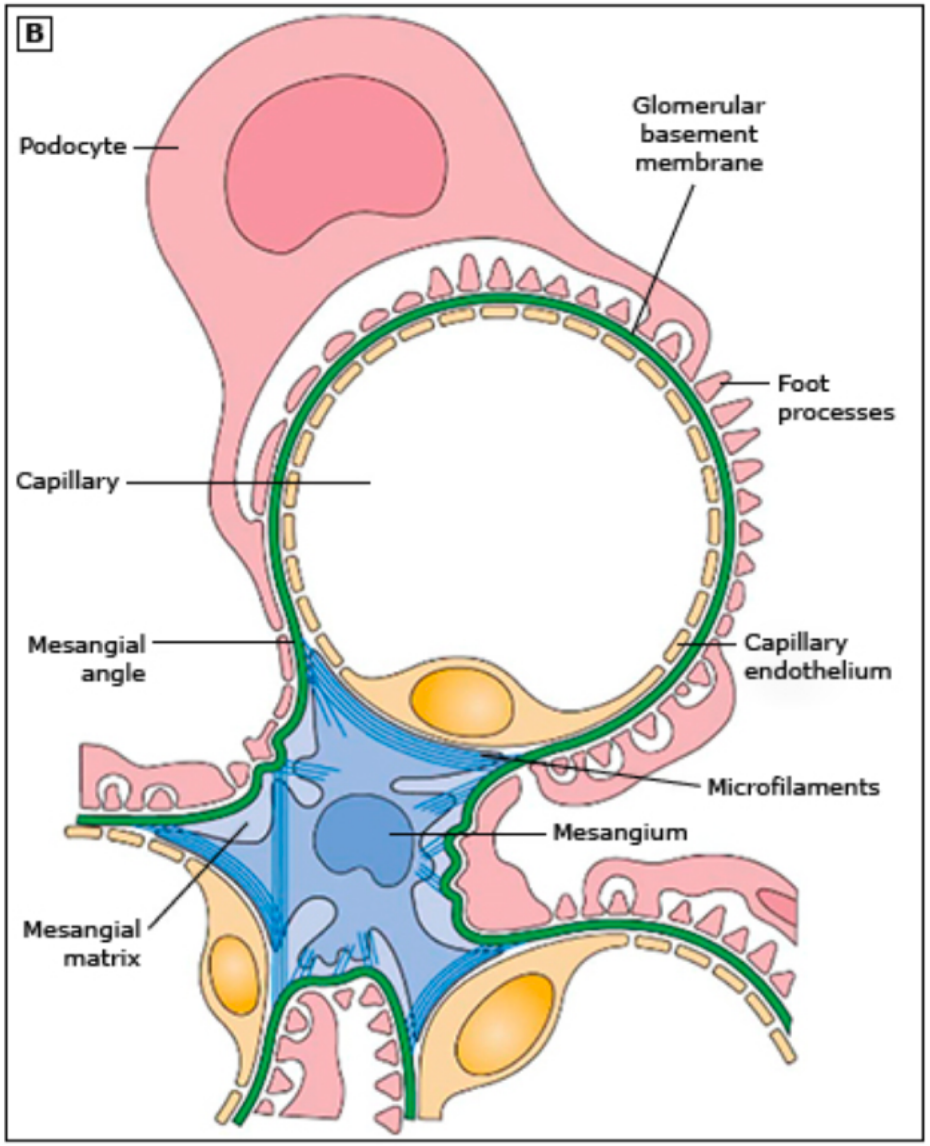


Diagram of glomerular anatomy



AA	Afferent arteriole	PE	Parietal epithelium
MD	Macula densa	PO	Podocyte
EGM	Extraglomerular mesangium	M	Mesangium
EA	Efferent arteriole	E	Endothelium
N	Sympathetic nerve terminals	F	Foot process
GC	Granular cells	GBM	Glomerular basement membrane
SMC	Vascular smooth muscle cells	US	Urinary space



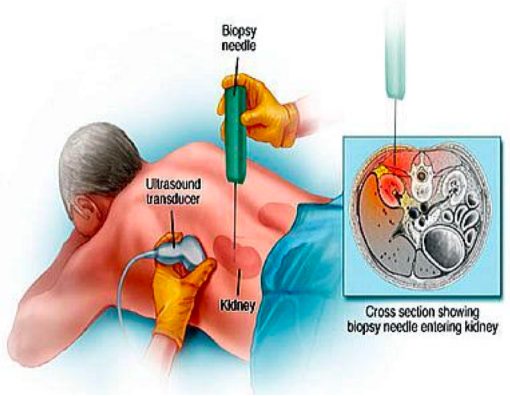
Types of Proteinuria

Proteinuria Classification	Pathogenesis	Clinical Setting	Level of proteinuria
Glomerular	Increased filtration of macromolecules (albumin)	Primary or systemic diseases	Variable
Overflow	Increased filtration (causing decreased reabsorptive capacity) or marked overproduction	Myeloma, hemolysis, rhabdomyolysis	Variable
Tubulointerstitial	Increased excretion of low molecular weight proteins (B2 macroglobulin) from decreased proximal tubule absorption	Interstitial inflammation/injury, heavy metal intoxication	<3 gr/day
Post-Renal Proteinuria	Inflammation of urinary tract. Non-albumin protein	UTI's, nephrolithiasis, GU tumor	<1 gr/day

Back to Mr Jones…
Next steps of work up

- HbA1C
- Anti-PLA2R autoantibody
- ANA and dsDNA antibody
- Serum C3 and C4 levels
- HBV, HCV, HIV
- In patients older than 50 years – serum free light chains and serum protein immunofixation

→KIDNEY BIOPSY



Nephrotic Syndrome - DD

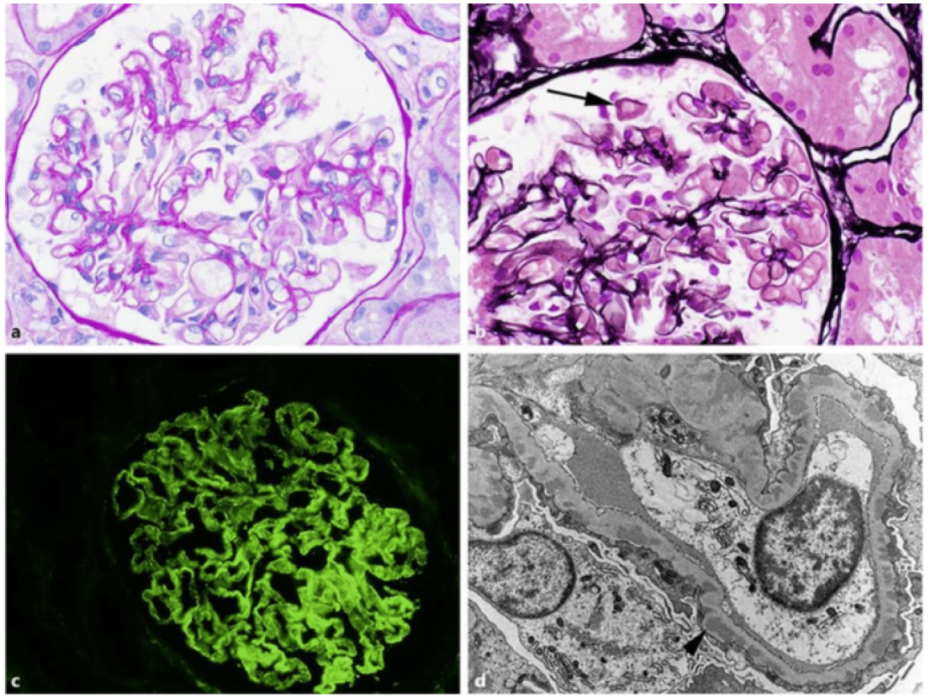
Systemic Diseases

- Diabetes Mellitus
- Lupus Nephritis
- Amyloidosis

Primary Diseases of the Kidney

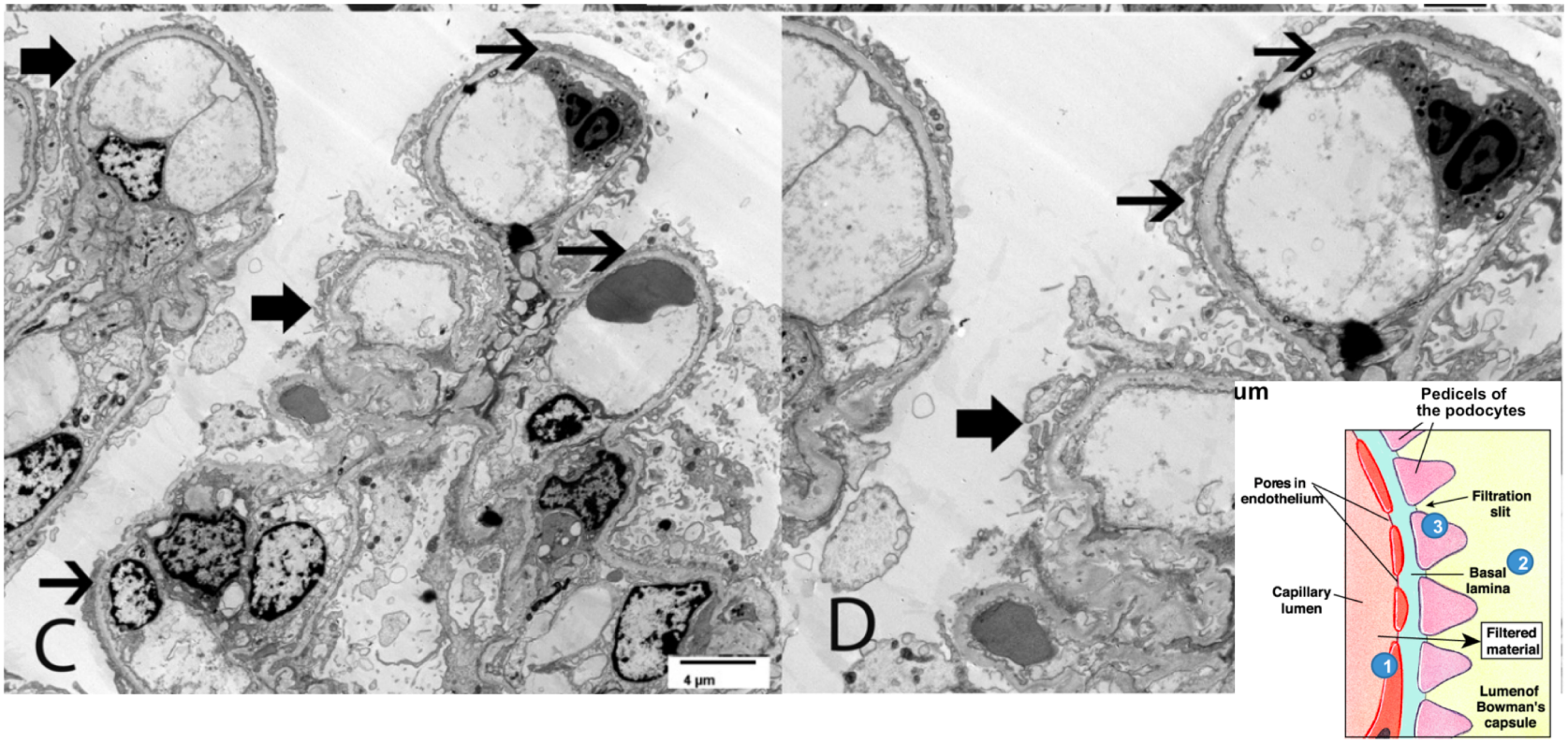
- Membranous Nephropathy
- Minimal Change Disease
- Focal Segmental Glomerulosclerosis (FSGS)

Kidney Biopsy



Membranous Nephropathy

Kidney Biopsy from a different story



An S. De Vriese.. Richard J. Glassock, and Fernando C. Fervenza *Differentiating Primary, Genetic, and Secondary FSGS in Adults: A Clinicopathologic Approach.*
J Am Soc Nephrol 29: 759-774, 2018

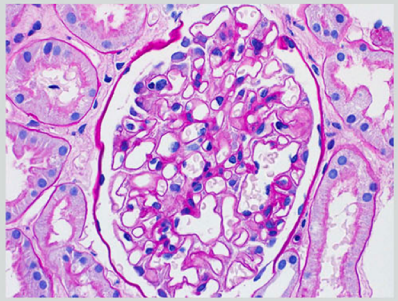
Membranous Nephropathy

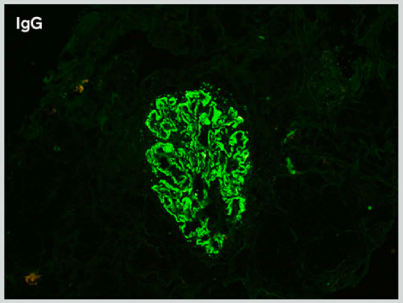
About 70%–80% of membranous nephropathy are classified as primary

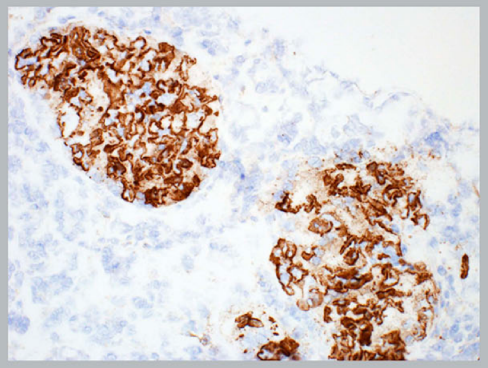
The remaining 20-30% have secondary forms associated with autoimmune diseases, infections, drug exposure, or malignancy

Identification of the two target antigens PLA2R and THSD7A allowed the development of serologic tests for circulating **anti-PLA2R** or **anti-THSD7A** autoantibodies, and revolutionized the diagnosis and follow up

PLA2R-Positive Membranous Glomerulonephritis:
KDIGO Recommendations for Serum Anti-PLA2R Testing







PLA2R-positive
by immunohistochemistry

KDIGO recommends serial measurement of serum anti-PLA2R antibodies (for research protocols)

Goal is to assess value of these biomarkers in determining spontaneous remission, treatment response, and prognosis

KDIGO Clinical practice guideline for glomerulonephritis..
Kidney International Supplement Vol. 2, Issue 2, June 2012 pp. 191

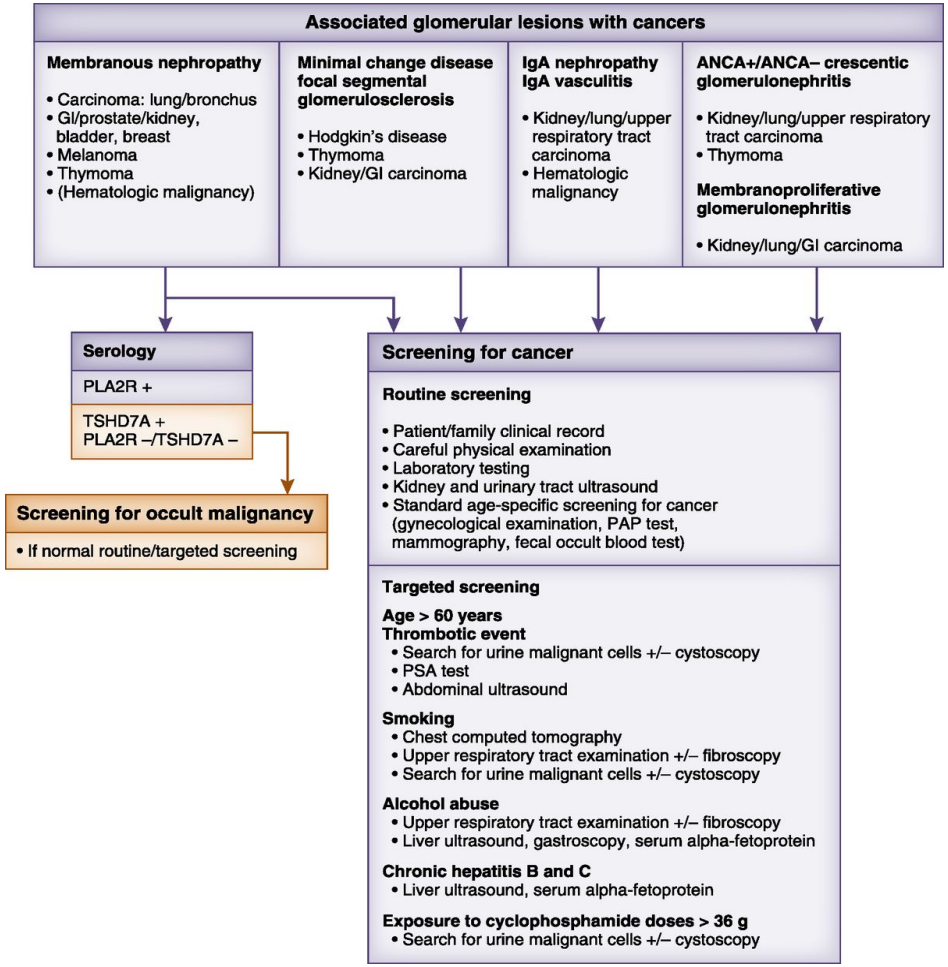
Arkana Laboratories

Cancer Screening

Standard cancer screening is recommended in all patients with glomerular lesions which may be associated with malignancy

Targeted screening tests must be additionally performed according to each patient's specific risk factors for cancer

Routine and targeted cancer screening in patients with glomerulopathy



CJASN

Thromboembolism

Patients with the nephrotic syndrome are at increased risk for venous thrombosis, particularly **deep vein thrombosis** and **renal vein thrombosis**

There is also increased risk of arterial thrombosis and pulmonary emboli

The risk of thrombosis is inversely related to the serum albumin levels

Prophylactic anticoagulation?

When? Albumin < 2.5 g/dL

Who?

- Membranous Nephropathy
- Pregnant patients

Proteinuria without Nephrotic Syndrome

- Isolated proteinuria?
  - No HTN
  - No hematuria
  - No systemic disease
  - No kidney injury/ azotemia

Transient Proteinuria

- Common, especially in young individuals
- Causes: fever, exercise, acute illness (eg URI), hyperglycemia
- Usually < 1 gram/ day
- Test: UACR or UPCR over 1-3 months
- Avoid exercise 24-48 hours prior to test
- Diagnosis is made when repeat test is no longer positive for proteinuria

Orthostatic Proteinuria

- Increased protein excretion in the upright position but normal protein excretion when the patient is supine
- Relatively **common in adolescents** (up to 5%), but uncommon in adults > 30 years old
- Usually < 1 gram/ day
- **Benign**, but kidney function and proteinuria should be followed yearly
- NORMAL early morning sample (<30mg), with positive PM sample within 24 hours = orthostatic proteinuria

Nephritic Syndrome

→ Glomerular Inflammation

- Hematuria
- Proteinuria – **can be in the nephrotic range**
- HTN
- Kidney injury
- Involvement of other organs

Nephritic Syndrome - DD

Systemic

- ANCA vasculitis (pauci-immue glomerulonephritis)
- Anti-GBM disease
- SLE
- IgA nephropathy
- TMA

Infections

- Bacterial – Strep/ staph
- Viral – HBV, HCV, CMV
- Parasitic – Plasmodium malariae

Proteinuria - What is the big deal?

- The degree of proteinuria is prognostically important in patients with primary and secondary glomerular diseases
- Higher degrees of proteinuria are associated with a more rapid progression to kidney failure, even in the absence of nephrotic syndrome

Relative risks of Major Complications of CKD

Ranking of adjusted relative risk

- Rank numbers 1-8
- Rank numbers 9-14
- Rank numbers 15-21
- Rank numbers 22-28

Absolute risk can be computed by multiplying the RRs in each cell by the incidence rate in the reference cell.

All-cause mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90-105	Ref	1.4	1.5	3.1
eGFR 75-90	1.0	1.3	1.7	2.3
eGFR 60-75	1.0	1.4	1.8	2.7
eGFR 45-60	1.3	1.7	2.2	3.6
eGFR 30-45	1.9	2.3	3.3	4.9
eGFR 15-30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

Kidney failure (ESRD)

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	Ref	Ref	7.8	18
eGFR 90-105	Ref	Ref	11	20
eGFR 75-90	Ref	Ref	3.8	48
eGFR 60-75	Ref	Ref	7.4	67
eGFR 45-60	5.2	22	40	147
eGFR 30-45	56	74	294	763
eGFR 15-30	433	1044	1056	2286

Acute kidney injury (AKI)

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	Ref	Ref	2.7	8.4
eGFR 90-105	Ref	Ref	2.4	5.8
eGFR 75-90	Ref	Ref	2.5	4.1
eGFR 60-75	Ref	Ref	3.3	6.4
eGFR 45-60	2.2	4.9	6.4	5.9
eGFR 30-45	7.3	10	12	20
eGFR 15-30	17	17	21	29

Progressive CKD

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	Ref	Ref	0.4	3.0
eGFR 90-105	Ref	Ref	0.9	3.3
eGFR 75-90	Ref	Ref	1.9	5.0
eGFR 60-75	Ref	Ref	3.2	8.1
eGFR 45-60	3.1	4.0	9.4	57
eGFR 30-45	3.0	19	15	22
eGFR 15-30	4.0	12	21	7.7

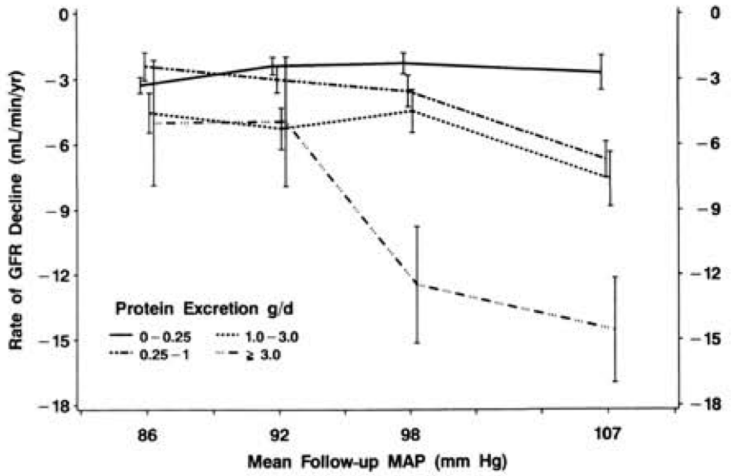
Treatment

- Optimal HTN control: Aim BP < 130/80
- Add a diuretic for optimal HTN management
- ACEi/ARB
- Other agents that reduce proteinuria: non-dihydropyridine Ca Channel blockers, mineralocorticoid antagonists
- SLGT-2 inh

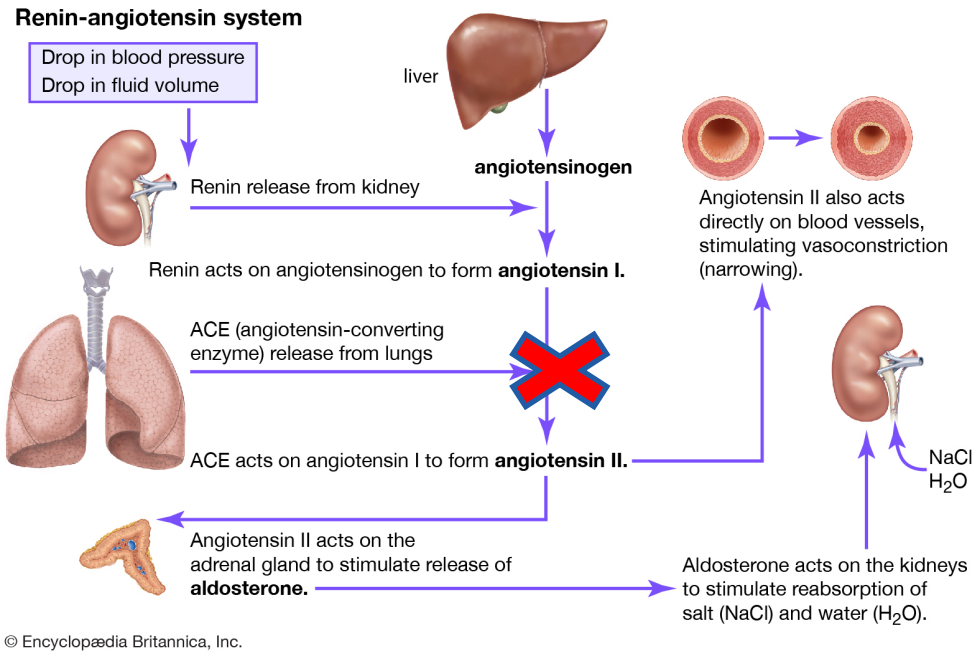
- Treatment for glomerular disease - IS

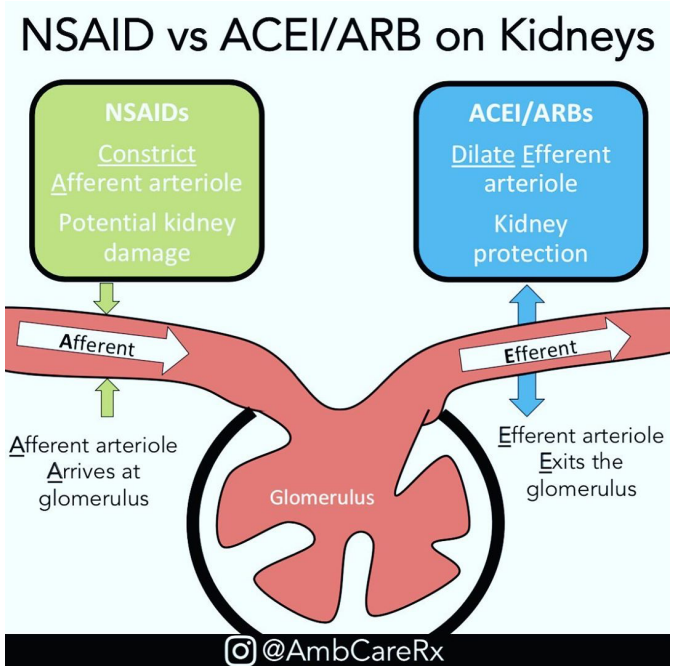
ACEi and ARB Therapy

- MDRD study *(Annals Int Med, 1995)*
- Proteinuria is independent risk factor for CKD progression
- Tight BP control reduces proteinuria and reduces GFR decline



Mechanism of ACE-inhibitors





Spironolactone/Eplerenone

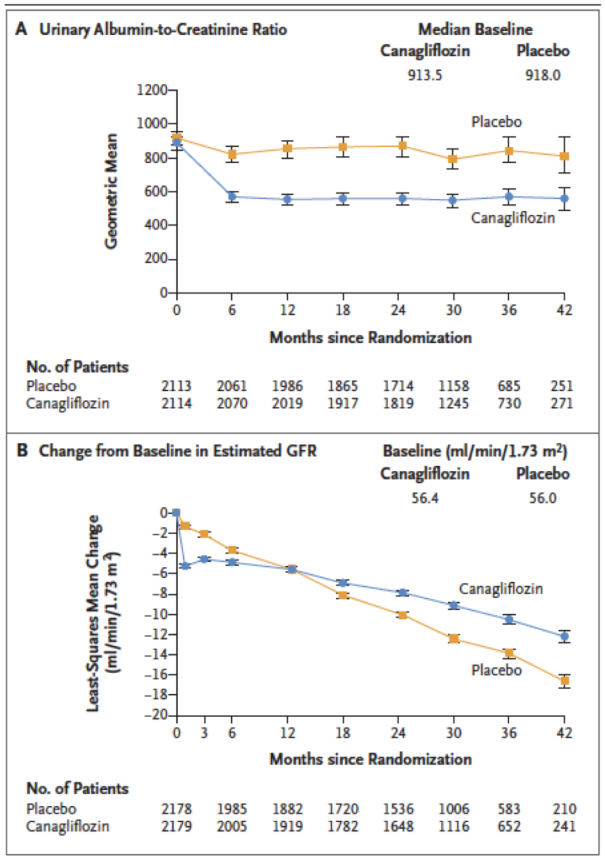
- Metanalysis *(CJASN 2009)* looked at MCA (Spironolactone 25mg daily) with ACEi compared to ACEi alone
- Proteinuria and HTN control improved significantly more with MCA + ACEi group
- No difference in GFR preservation between groups
- Higher risk Hyperkalemia with MCA+ACEi

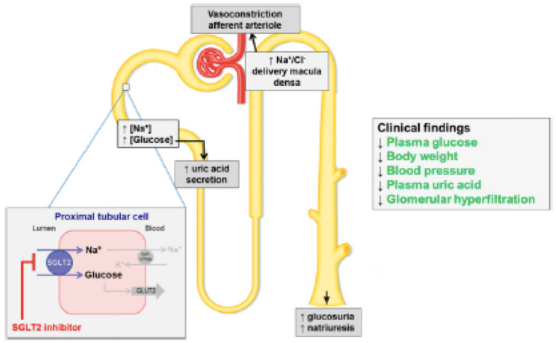
SLGT-2 inhibitors

- CREDENCE trial (NEJM 2019) double blind randomized trial, type II DM + albuminuria +CKD
- Canagliflozin 100mg daily or placebo
- All patients GFR 30-90, treated with RAAS blockade

- **Diabetic patients with >300mg albuminuria despite ARB/ACEi should start a sodium-glucose co-transporter (SGLT-2inh)**

SLGT-2 inhibitors



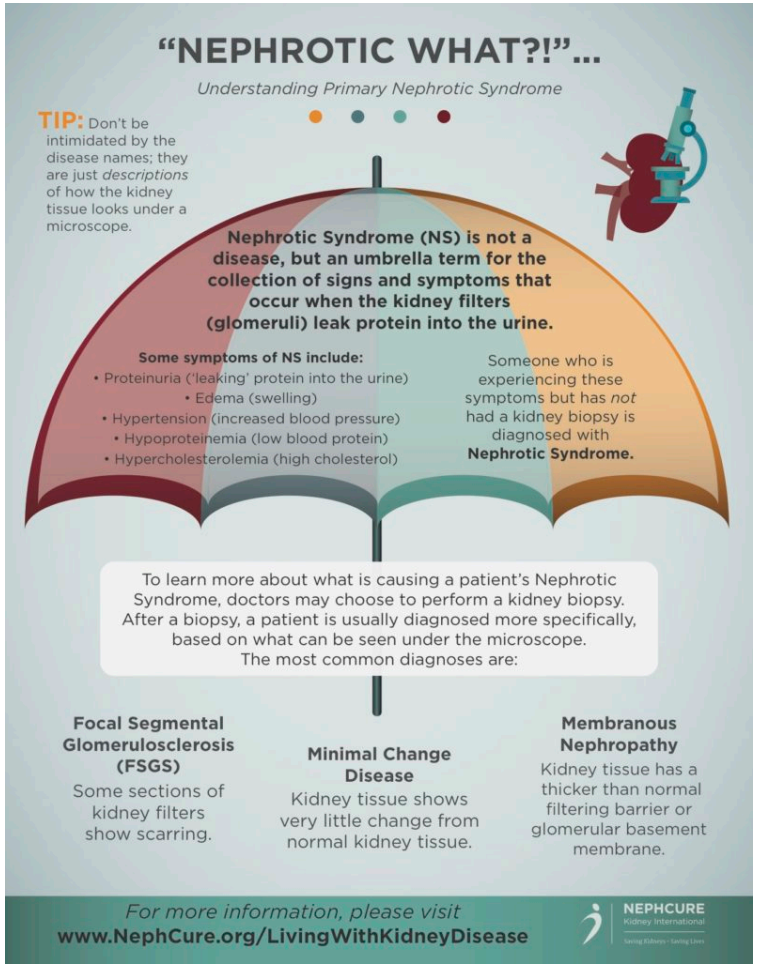


Take home message

- Even within the normal range, higher amounts of albuminuria are associated with an increased risk of cardiovascular disease
- For patients who are very likely to have nephrotic-range proteinuria due to diabetic nephropathy, biopsy can be deferred
- Treat underlying cause/risk factors: obesity/DM/HTN/smoking/HL

Take home message - 2

- Start RAAS blockade: don't wait! can start in CKDG1-G3b safely. **Expect 30% rise in creat which stabilizes**
- With treatment, aim to reduce albuminuria as much as possible by up-titrating RAAS blockade to achieve maximum effect to delay CKD progression
- For type 2 DM, with eGFR > 45, and > 300mg albuminuria, NOT on insulin/sulfynurea, START SGLT-2 inh at lowest dose. **Expect 30% rise in creatinine which stabilizes**


"NEPHROTIC WHAT?!"...
Understanding Primary Nephrotic Syndrome
TIP: Don't be intimidated by the disease names; they are just descriptions of how the kidney tissue looks under a microscope.
Nephrotic Syndrome (NS) is not a disease, but an umbrella term for the collection of signs and symptoms that occur when the kidney filters (glomeruli) leak protein into the urine.
Some symptoms of NS include:
• Proteinuria ('leaking' protein into the urine)
• Edema (swelling)
• Hypertension (increased blood pressure)
• Hypoproteinemia (low blood protein)
• Hypercholesterolemia (high cholesterol)
Someone who is experiencing these symptoms but has not had a kidney biopsy is diagnosed with Nephrotic Syndrome.
To learn more about what is causing a patient's Nephrotic Syndrome, doctors may choose to perform a kidney biopsy. After a biopsy, a patient is usually diagnosed more specifically, based on what can be seen under the microscope. The most common diagnoses are:
Focal Segmental Glomerulosclerosis (FSGS)
Some sections of kidney filters show scarring.
Minimal Change Disease
Kidney tissue shows very little change from normal kidney tissue.
Membranous Nephropathy
Kidney tissue has a thicker than normal filtering barrier or glomerular basement membrane.
For more information, please visit
www.NephCure.org/LivingWithKidneyDisease
NEPHCURE
Kidney International

Thank you!

- Questions?

Jefferson

Philadelphia University +
Thomas Jefferson University